after "April 11, 1985," insert --(now abandoned)--,

after "January 2, 1985," insert --(now abandoned)--.

Page 11, first line, after "1985," insert --(now abandoned), and Serial No. 878,045, filed June 24, 1986, and now issued as U. S. Patent No. 4,849,513--.

Page 11, line 17, change "maybe" to --may be--.

Page 19, line 29, change "hydroxzide" to --hydroxide--.

REMARKS

Reconsideration is requested in view of the foregoing amendments, and the following remarks.

On October 13, 1988 in Serial No. 106,232 a "Petition and Amendment Under Rule 48," together with other related documents were filed in this patent application, seeking to have the name of Charles R. Connell added as a joint inventor. We find no acknowledgement regarding receipt of these papers or any discussion of their disposition in the Office Action. Clarification is requested.

The claims are 15 to 22 and 36 to 38.

Claims 31 - 35 and 39 to 44 were cancelled without prejudice by amendment mailed on July 2, 1992 which crossed in the mail with

the outstanding Office Action.

Claims 15 to 22 are allowed.

The typographical errors have been corrected.

The status of the parent and earlier filed patent applications referred to in the Specification has been provided.

The requirement for the submission of new drawings is noted. This requirement may be fulfilled at any time up to 3 months after the Notice of Allowability. Applicants are preparing and will file new drawings within that time period.

Claims 36 to 38 were rejected and the Specification objected to under 35 USC 112, first paragraph.

The Examiner argues that only a system comprising four chromophores with distinct spectral characteristics is enabled by the Specification.

The rejection and objection should be withdrawn for the following reasons.

The disclosed invention pertains to the use of fluorophores or chromophores to tag oligonucleotide fragments and use them to

determine the nucleotide sequence in DNA and similar molecules. There are, of course, up to four different nucleotides present to be detected. Claims 36 to 38 are drawn to the "classical" case to which the present invention preferably applies, viz., the use of four tags, each being distinguishable from the others by its spectral characteristics to sequence DNA segments. The enablement provided by the Specification is not limited to the "classical" case, and is enabling for the detection of just the one type (out of the four) nucleotide present in the oligonucleotide being sequenced. The advantages of the present invention obtain in such a process just as they do in the "classical" case. The Specification is admitted sufficient for the "classical" case, and is equally enabling for the simpler case which is but a subset of the "classical" case. The Specification describes the means to readily and in an automated way detect A,G,C and T nucleotides. This enablement clearly constitutes an enablement of any one or all four of the nucleotides. The disclosure of detecting A, G, C and T is clearly an enabling disclosure of the detection of any one of A, G, C or T. The foregoing argument is submitted for completeness. However, the arguments in the Office Action are inapplicable to claims 36-38 since these claims are drawn to the classical case. Frankly, we are at a loss to understand why claims 36 to 38 were rejected, given the nature of the Examiner's arguments.

In any case, the present Specification is more than adequate as an enablement of the claimed invention of claims 36 to 38. The

objection to the Specification and the related rejection of claims 36 to 38 should be withdrawn.

Claims 36 - 38 were rejected on Kaplan, U.S. Patent 4,151,065 and the Maxim/Gilbert and Sanger prior art discussed in the Specification in view of Khanna et al., U. S. Patent No. 4,151,065 and Ward, U.S. Patent 4,711,955. Kaplan relates to a horizontal slab gel electrophoresis apparatus having compartments for vertical wicks at each end of a horizontal trough or tray 30. Adjacent to the vertical wicks are vertical buffer compartments with built in electrodes. A partition separates the vertical wicks from the buffer compartment and includes a slot to permit communication between the buffer and the gel slab. Kaplan discloses the separation of DNA fragments on the gel, column 7, lines 29 et seq. There is no suggestion in Kaplan of sequencing the DNA. Kaplan is fundamentally deficient as a primary reference.

The tray 30 can be made of a material which transmits ultraviolet light, column 3, lines 5-10 and lines 47-49. However, there is no suggestion in this of either sequencing or labeling.

According to this invention, an important and major advance over the prior art of Maxim/Gilbert and Sanger has been achieved.

The Maxim/Gilbert and Sanger prior art is not suggestive of

the present invention. As is pointed out in the Specification, Maxim/Gilbert and Sanger each employed radiolabels.

In the practice of the present invention, the reaction mixtures are combined and electrophoresed together. The separated bands of DNA are then detected by their fluorescence as they pass out the bottom of the tube, and the sequence of their colors directly yields the base sequence. A major result of this fluorescence detection method is that it can readily be automated. This invention has made it possible to begin to sequence extensive stretches of the human genome, which contains $3x10^9$ base pairs. The prior art method using autoradiograms requires contact with the gel and is too slow to enable full scale analysis of the human genome.

The avoidance of radiolabels is beneficial from a health and environmental standpoint. Moreover, the present invention also provides major advances in the art which are in no way health or environmentally related. A major result of the present invention is that it can readily be automated. The sequencing of the entire human genome has now become feasible. These major advances provided by this invention are indicative of its non-obviousness.

It is true that colored labels and fluorescent labels have been known and used in other processes. These facts serve to demonstrate that the present invention was not obvious to those

skilled in the art for, had the use of colored, fluorescent and similar labels been obvious to use in DNA sequencing, it would have been done long ago. The benefits of using these labels in DNA sequencing are undeniable, and so desirable that everyone would have jumped on the colored label-fluorescent label handwagon many years ago, had it been obvious to do so. These circumstances are powerful evidence that the present invention was not obvious.

Khanna et al. disclose a class of di(chalcogen ether) symmetrically substituted fluorescein compounds which are disclosed, column 2, line 45, to be useful when conjugated to polypeptides or to solid or soluble supports for use in diagnostic immunoassays. Ward relates to a nucleotide or oligo- or polynucleotide sequence comprising at least one of a moiety having a 7-deazapurine or a pyrimidine substituent and a moiety selected from the group consisting of biotin and iminobiotin. Neither of these patents is at all pertinent to the present invention and suggest nothing at all in relation to DNA sequencing. Basically, Khanna et al, Ward, Maxim/Gilbert and Sanger logically add nothing to the Kaplan patent.

The combination of Khanna et al, Ward and Kaplan which is proposed in the Office Action is based on careful selection and amounts to a reconstruction of these three patents (together with Maxim/Gilbert and Sanger) in a way which is suggested only by

applicants' Specification. This hindsight reconstruction of the prior art brings to mind a very appropos and recent decision of the Federal Circuit, Gillette Co. v. S.C. Johnson & Son, Inc., 919 F2d 720, 16 USPQ 2d 1923 (Fed. Cir. 1990) where the Court said:

> "The inappropriatness of hindsight as a test of obviousness was, in point of fact, discovered, and articulated lucidly, over three centuries ago, by Milton, who, in Paradise Lost, Part IV, L. 478-501, stated, in dictum:
>
> > The invention all admired, and each how he
> > To be the inventor missed; so easy it seemed,
> > Once found, which yet unfound most would have thought,
> > Impossible!"

The present invention represents a major advance in the art of DNA sequencing. The proper approach to the obviousness issue must start with the claimed invention as a whole. Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d 1437, 1448 [223 USPQ 603, 609-10] (Fed. Cir. 1984). The invention as a whole embraces the structure, its properties and the problem it solves. In re Wright, 848 F.2d 1216, 1219 [6 USPQ2d 1959, 1961-62] (Fed. Cir. 1988). The determination of whether a novel structure is or is not "obvious" requires cognizance of the properties of that structure and the

problem which it solves, viewed in light of the teachings of the prior art. Id.

An invention is not obvious merely because it is a combination of old elements each of which was well known in the art at the time the invention was made. Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d at 1448 [223 USPQ at 609]; Reiner v. I. Leon Co., 285 F.2d 501, 503 [128 USPQ 25, 27] (2d Cir. 1960). Rather, if such a combination is novel, the issue is whether bringing them together as taught by the patentee was obvious in light of the prior art. United States v. Adams, 383 U.S. 39, 50 [148 USPQ 479,483] (1966). The critical inquiry is whether "there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1558 [225 USPQ 26, 31] (Fed. Cir. 1985). (emphasis in original), citing Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 1462 [221 USPQ 481, 488] (Fed. Cir. 1984). In other words, obviousness "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." In re Fine, 837 F.2d 1071, 1075 [5 USPQ2d 1596, 1599] (Fed. Cir. 1988), quoting ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577 [221 USPQ 929, 933] (Fed. Cir. 1984).

"A patentable invention may lie in the discovery of the source

of a problem even though the remedy may be obvious once the source of the problem is identified." In re Sponnoble, 405 F.2d 578, 585 [160 USPQ 237, 243] (C.C.P.A. 1969).

The sequencing of large genomic segments has presented a daunting challenge to those skilled in the art. This problem has been solved by the present invention.

In the landmark case on obviousness, Graham v. John Deere, 383 U.S. 1 [148 USPQ 459] (1966), the Supreme Court articulated the following test:

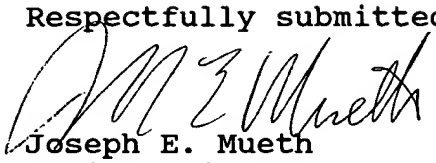
> "Under Sec. 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy."

The present invention clearly satisfies the requirements for a finding of non-obviousness.

The rejection of claims 36 - 38 on prior art should be withdrawn.

In the absence of more pertinent prior art, the Notice of allowance is requested.

Respectfully submitted,



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